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Thyroid-Iodide Therapy of Blastomycosis

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The use of iodides has been the standard form of therapy for the deep mycoses during the past half century. It has withstood well the test of time, not because it was remarkably effective, but rather because there were no remedies quite as good. For smaller localized lesions surgery could be used, and recently the stilbamidines became available and proved themselves potent remedies for blastomycosis. Nevertheless, iodide continues in use largely because of its availability, low cost, ease of administration, and relative harmlessness. Furthermore, its position in the treatment of the deep mycoses often justifies itself, as in the cutaneous forms of sporotrichosis, where the drug is almost regularly effective and curative.

The way iodide works against the deep mycoses remains unexplained. It is known to have little direct restraining power over *Sporotrichum schenckii*, as shown by survival of the organism in 10% solution.¹ Yet iodide is more or less a specific for sporotrichosis, at least when the skin alone is involved. Nor is it clear how these halogen salts dissolve gummas or act unfavorably at times on lesions of tuberculosis.

Investigators have disagreed about the amount of iodide partitioned in diseased tissue.² Most of them found increased quantities in acute experiments. Recently, Sternberg and co-workers,³ in a thorough and painstaking study using isotopes, found increased concentrations of iodide in granulomas of mice infected with either *Coccidioides immitis* or *S. schenckii*. When,

however, they used large pharmacologic doses, the various tissues, both infected and apparently normal, all contained similar concentrations of iodide, except for the thyroid and kidneys.

The principal action of iodide in body metabolism is to provide an essential ingredient of the thyroid hormones.⁴ The thyroid uses the halogen in a series of syntheses to form thyroglobulin. This protein complex, under the influence of thyrotropin, discharges thyroxin and triiodothyronine into the blood stream, whence they find their way to all tissues.

For many years clinicians have found iodide useful in treating thyroidal diseases. Paradoxically, the same drug can alleviate the contrasting states of myxedema and Graves' disease.⁵ It is thought that iodide in therapeutic doses helps to block the excessive release into the blood of thyroxin already formed in the thyroid. Conversely, iodide relieves goiter induced by insufficient quantities of the halogen in food and water.

In view of the relative innocuousness of iodide directly for deep mycotic organisms in vitro and the preeminent position of it in the thyroid alone of the organs of the body, it was felt that an approach to the treatment of blastomycosis through that gland might be fruitful. My first attempts were by blocking the thyroid through administration of antithyroid agents. These trials ended in near disaster. This experience led to use of the glandular products instead, with happier results.

Method of Use

For both localized cutaneous and systemic infections the essential method is the same. If there is no fever, the basal metabolism rate is determined. This is checked by thyroid iodide uptake. General physical examination is made, with special attention

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to the heart. Both thyroid and saturated solution of potassium iodide are given simultaneously. The latter may be begun with 15 drops three times daily with meals. The former is given in 0.065 gm. doses daily. The dosage of each is raised every fifth day, with 0.065 gm. of thyroid and 12 drops of iodide per day added to the last previous dosage until tolerance is reached. Eventually patients can usually take 0.259 to 0.518 gm. of thyroid and 50 to 100 drops of iodide solution per day. It is surprising how well these enormous quantities of both drugs are tolerated. If iodide intolerance develops in the form of the usual follicular pustules in seborrheic areas, it can usually be overcome by giving 3 to 10 drops of potassium arsenite solution (Fowler's solution) three times a day for a week or two without discontinuing the iodides. None of our patients developed any serious untoward effects from the halogen. If such effects should arise, the drug should be stopped and sodium and ammonium chlorides should be administered to hasten excretion. Excess iodide, unlike bromide, is removed from the body quickly, almost all within 48 hours. The heart rate and general physical examination govern the maximal dose of thyroid. We permitted a rise in pulse rate of 15 per minute, an arbitrary figure. In the systemic form, if the patient gained weight and was doing well, we permitted an increase of 20. A generous diet is encouraged, especially of protein. Blood counts, hemoglobin, and differential counts of white cells are made weekly, and at the same time the weight is determined.

Results

A total of nine of my patients, seven with cutaneous, and two with systemic infections, were studied. All the localized infections healed completely without recurrence. Somewhat uneven scars remained at the sites. Those with systemic infections appear to be clinically cured. A latent period occurred during the first three weeks of treatment, during which there was little change. When the lesions began to pale and flatten, involution of pustules from the concave side or center of circinate patches occurred. Strength and weight increases paralleled improvement in the appearance of the lesions. The smallest patches of the skin healed within six weeks, but the patients with systemic infections received treatment for as long as six months. The dosages were reduced after substantial improvement.

Three patients developed papulopustular eruptions; one of these had two separate such outbreaks. These eruptions were controlled with potassium arsenite solution without necessitating interruption of the general treatment. The complement-fixation test was positive in three patients. After cure, the tests became negative in all.

In addition to my nine cases, Dr. Leon Goldman sent me reports on two of his patients with blastomycosis. One had the cutaneous form, while the other had evidence of systemic infection. In both cases he employed the thyroid-iodide regimen with rather favorable results. Capt. John W. Albritten, too, reported to me his results on a case of treatment-resistant systemic sporotrichosis. His patient, too, had favorable effects from the administration of thyroid and iodide.

Illustrative Case Histories

CASE 1.—A Negro man, aged 34, worked at odd jobs and as janitor. He had a solid raised verrucous patch of dermatitis, 5 cm. at its greatest diameter, below the right scapula and a smaller lesion above the right clavicle from which Blastomyces were cultivated and shown directly. On the basis of reasoning discussed in the introduction, he was given 9.71 gm. of potassium iodide three times a day and, in addition, 50 mg. of propylthiouracil twice a day. Within five days the lesions enlarged and became more inflamed. It was obvious that the eruption was worse and that some ground had been lost. The propylthiouracil was stopped, and 0.065 gm. of thyroid was substituted for it. Five days later the thyroid dose was raised to 0.130 gm. and the potassium iodide, to 1.746 gm. a day. Two weeks later there was noticeable improvement in both lesions. The dosage was increased progressively during the first six weeks to 0.389 gm. of thyroid and 90 drops of iodide solution. The lesions became dry, pale, and flat, and two weeks later the crusts separated, leaving slightly depigmented, atrophic areas, somewhat smaller than the original lesions. The active treatment was continued 2 weeks longer, or a total of 10 weeks, and then stopped. There has been no recurrence in seven years nor any new formation of papules and pustules in the healed scars, as is often seen in blastomycosis.

CASE 2.—A white man, aged 44, a migratory worker from Mexico, had a crusted lesion on the right eyelid, 0.75 cm. in diameter, several similar

lesions on the face and neck, and one on the right shoulder. His physical condition was good; basal metabolism was -6% . His treatment started with 0.065 gm. of thyroid and 2.910 gm. of potassium iodide per day. The dosage of each was raised progressively. After four weeks' treatment there was a diffuse papulopustular follicular eruption on the forehead, chest, and back. The eruption was thought to be due to iodides. Potassium arsenite solution, 3 to 8 drops, three times a day, was given additionally for 10 days. The follicular eruption then disappeared. The blastomycosis lesions healed after three and one-half months, during most of which time he was taking 0.324 gm. of thyroid and 6.402 gm. of potassium iodide daily. Some of the lesions left uneven scars, but they were supple and without a trace of activity.

CASE 3.—A white man, age 62, jobless but previously a tenant farmer, had several lesions, averaging 6 cm. in diameter, on the right arm, back, lower abdomen, and thighs. Blastomyces organisms were found by culture and by immediate preparations in potassium hydroxide solution. Except for evidence of poor nutrition, his physical examination showed nothing abnormal. The basal metabolic rate was -10% , and his iodine uptake at the lower level was considered euthyroid. With treatment his lesions improved progressively, and the last one, over the pubis, healed after four and one-half months. At that time he took 0.259 gm. of thyroid and 135 drops of potassium iodide solution. We followed his condition for two months, when he disappeared. There was no recurrence during the latter period.

CASE 4.—A Negro youth, aged 19, had several small coin-sized lesions on the face and neck for a month before examination. Before the lesions appeared, he had a dry unproductive cough and pain in the left chest. There was dullness at this site, and x-rays showed a diffuse density. Large patches of tinea versicolor appeared on the chest and back. Blood and urine examinations showed nothing abnormal. Sputum was negative for tubercle bacilli and Blastomyces. Blastomycin, 1:1000, gave a 4+ reaction in 48 hours, and coccidioidin, 1:100, a negative one. Thoracentesis yielded a small amount of bloody material showing yeasts. Culture showed presence of Blastomyces dermatitidis. Tissue from a biopsy of a skin lesion also contained yeast cells and grew Blastomyces. Blood culture was negative. In addition, Blastomyces organisms were recovered from a prostatic smear.

Treatment began and continued according to the usual plan. The highest dose of thyroid was 0.389 gm. and 90 drops of potassium iodide solution daily. At first the patient lost weight and had a pulse rate of 96-104. It was felt that part of this elevated rate was due to a fever of 101 F, and it did

not alarm me. A month after the beginning of therapy the skin lesions were much improved and the crusts began to separate, but after two months several large cherry-sized elevations appeared on both sides of the neck. These were enlarged nodes. Biopsy of one grew dermatitidis. A follicular eruption of papules and pustules on the face and upper trunk appeared. Potassium arsenite solution, 5 drops three times a day, was given for two weeks. The drug eruption cleared. Six months after the beginning of treatment the lymph node enlargements flattened and at biopsy showed no organisms. All skin lesions had healed, leaving smooth scars. Chest x-ray showed only a residual pleural thickening of the costophrenic sinus. Cultures of prostatic massage material grew no fungi. The patient looked and felt well and gained 15 lb. Fever and cough were gone after four months. After six months of treatment we considered him clinically cured. There has been no evidence of recurrence during the past two years of observation. His complement-fixation test, which previously was positive, 1:250, became negative and has remained so.

Comment

Since iodide solutions in high concentration in vitro are not lethal to Blastomyces, the logical attack on the fungus is through the thyroid. This supposition was supported by the unfavorable and near-disastrous results that followed when the antithyroid agent propylthiouracil was used. The hormones of the thyroid are utilized by all organs, tissues, and cells. These glandular products are important in governing the rate of metabolic activity. Just how they influence immunity is not clear. Further basic studies will no doubt show some relationship. Many studies have failed to show thyroxin to be a catalyst or to enhance the action of known catalysts. For the present, the fundamental mechanism of action of the thyroid hormone is completely unknown. It is true, of course, that thyroid hormone increases oxygen consumption of tissues.

Practically all the circulating iodine is present in organic form and represents, for the most part, thyroid hormone in transit from gland to tissues.⁴ More recent evidence indicates that most of the hormone is present in the β -globulin fraction. Practically nothing is known of the

form of the organic iodine present in the tissues, although it presumably occurs as thyroxine and triiodothyronine. In pharmacologic doses Sternberg and co-workers³ found that normal and infected tissues, except thyroid and kidney, of animals took up similar concentrations of iodide.

It has been observed that infected drinking water produces goiter.⁴ Certain foods and substances, too, are known to act as goitrogens. Cabbage, cauliflower, and Brussels sprouts are known to be goitrogenic. This action is due not to a lack of iodine in the diet but to an increased demand for iodine. Administration of iodide corrects the effects of these goitrogens.

It may be postulated that the organisms of the deep mycoses, too, act as goitrogenic agents. The basal metabolism in those of our patients in whom it was determined was found to be at the lower level of the normal range. The administration of iodine might overcome this increased demand for the halogen. Sternberg and his collaborators³ found that the thyroids of their animals that were infected with *C. immitis* and *S. schenckii* took up significantly less iodide than the thyroids in control animals.

The administration of thyroid would dispense with the need for iodine in making intrinsic thyroid hormones. I have not tried thyroid administration alone, without iodide, in the deep mycotic infections. This should be done to improve our understanding of the problem. Practically, however, it is desirable to maintain the patient's own thyroid gland by supplying its need for basic material. It is planned in future studies to repeat Sternberg's work and make observations on the thyroid uptake of iodine under the influence of deep mycotic infections. Iodide exerts no influence on the peripheral action of thyroid hormones.⁵ Thus, thyrotoxicosis produced by giving large amounts of thyroid hormone is uninfluenced by the administration of the ion. This points to a direct action on the thyroid gland only.

The clinical results reported here would seem to show that thyroid administration enhances the effects of iodide in blastomycosis. There are insufficient data to clarify how this is accomplished. For that purpose much further investigation is needed. Perhaps the major work can be done with use of laboratory animals susceptible to infection with *B. dermatitidis*, but the final and convincing proofs must be demonstrated in humans with natural and spontaneous infections.

Summary

Thyroid and iodide were administered to nine patients with blastomycosis. Seven had cutaneous and two had systemic types of infection. All were clinically cured. Two other patients with blastomycosis and one with systemic sporotrichosis were treated with thyroid and iodide by colleagues and were reported to be favorably influenced. The rationale of this form of therapy and basic considerations of pharmacology and physiology of the thyroid gland, of its hormones, and of iodine are discussed.

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REFERENCES

1. Henrici, A. T.: *Molds, Yeasts, and Actinomycetes*, Ed. 2, edited by C. E. Skinner, C. W. Emmons, and H. M. Tsuchiya, New York, John Wiley & Sons, Inc., 1947, p. 137.
2. Wallace, G. B., and Brodie, B. B.: The Distribution of Administered Iodide and Thiocyanate in Comparison with Chloride in Pathological Tissues, and Their Relation to Body Fluids, *J. Pharmacol. & Exper. Therap.* 61:412, 1937.
3. Sternberg, T. H.; Newcomer, V. D.; Steffen, C. G.; Fields, M., and Libby, R. L.: The Distribution of Radioactive Iodine (I-131) in Experimental Coccidioidomycosis and Sporotrichosis, *J. Invest. Dermat.* 24:397, 1955.
4. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, Ed. 5, Baltimore, The Williams & Wilkins Company, 1950.
5. Goodman, L. S., and Gilman, A. Z.: *The Pharmacological Basis of Therapeutics*, Ed. 2, New York, The Macmillan Company, 1955.